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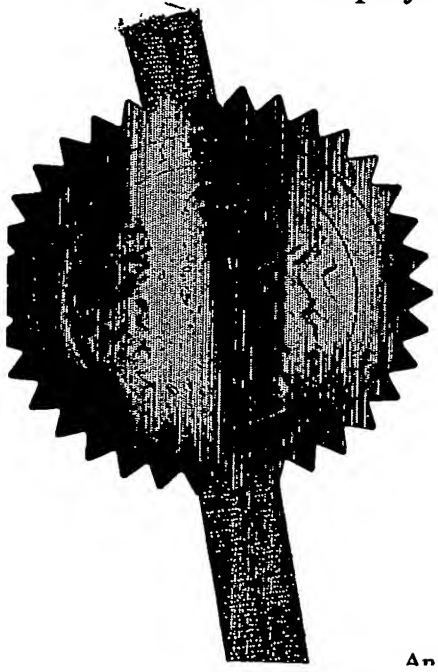

Signed P. Mahoney

Dated 25 March 2004

Patents Form 1/77

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The Patent Office
Cardiff Road
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1. Your reference — MG/JW/PB60228P

2. Patent application number
(The Patent Office will fill in his part) — 0309221.0 — 23 APR 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

United Kingdom 4735870003

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS 8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
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Continuation sheets of this form	
Description	22
Claim(s)	2
Abstract	
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature M Gibson Date 23-Apr-03

12. Name and daytime telephone number of person to contact in the United Kingdom

M Gibson 01279 644841

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NOVEL COMPOUNDS

The present invention relates to novel hydroxyethylamine compounds having Asp2 (β-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated β- amyloid levels or β-amyloid deposits, particularly Alzheimer's disease.

Alzheimer's disease is a degenerative brain disorder in which extracellular deposition of Aβ in the form of senile plaques represents a key pathological hallmark of the disease (Selkoe, D. J. (2001) Physiological Reviews **81**: 741-766). The presence of senile plaques is accompanied by a prominent inflammatory response and neuronal loss. β-amyloid (Aβ) exists in soluble and insoluble, fibrillar forms and a specific fibrillar form has been identified as the predominant neurotoxic species (Vassar, R. and Citron, M. (2000) Neuron **27**: 419-422). In addition it has been reported that dementia correlates more closely with the levels of soluble amyloid rather than plaque burden (Naslund, J. *et al.* (2000) J. Am. Med. Assoc. **12**: 1571-1577; Younkin, S. (2001) Nat. Med. **1**: 8-19). Aβ is known to be produced through the cleavage of the beta amyloid precursor protein (also known as APP) by an aspartyl protease enzyme known as Asp2 (also known as β-secretase, BACE1 or Memapsin) (De Strooper, B. and Konig, G. (1999) Nature **402**: 471-472).

Therefore, it has been proposed that inhibition of the Asp2 enzyme would reduce the level of APP processing and consequently reduce the levels of Aβ peptides found within the brain. Therefore, it is also thought that inhibition of the Asp2 enzyme would be an effective therapeutic target in the treatment of Alzheimer's disease.

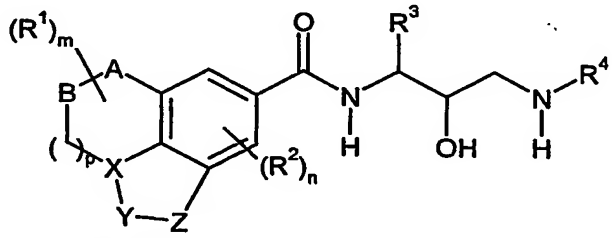
APP is cleaved by a variety of proteolytic enzymes (De Strooper, B. and Konig, G. (1999) Nature **402**: 471-472). The key enzymes in the amyloidogenic pathway are Asp2 (β-secretase) and γ-secretase both of which are aspartic proteinases and cleavage of APP by these enzymes generates Aβ. The non-amyloidogenic, α-secretase pathway, which precludes Aβ formation, has been shown to be catalysed by a number of proteinases, the best candidate being ADAM10, a disintegrin and metalloproteinase. Asp1 has been claimed to show both α- and β-secretase activity *in vitro*. The pattern of expression of Asp1 and Asp2 are quite different, Asp2 is most highly expressed in the pancreas and brain while Asp1 expression occurs in many other peripheral tissues. The Asp2 knockout mouse indicates that lack of Asp2 abolished Aβ production and also shows that in this animal model endogenous Asp1 cannot substitute for the Asp2 deficiency (Luo, Y. *et al.* (2001) Nat Neurosci. **4**: 231-232; Cai, H. *et. al.* (2001) Nat Neurosci. **4**: 233-234; Roberds, S. L. *et al.* (2001) Hum. Mol. Genet. **10**: 1317-1324).

For an agent to be therapeutically useful in the treatment of Alzheimer's disease it is preferable that said agent is a potent inhibitor of the Asp2 enzyme, but should ideally also be selective for Asp2 over other enzymes of the aspartyl proteinase family, e.g Cathepsin D (Connor, G. E. (1998) Cathepsin D in Handbook of Proteolytic Enzymes, Barrett, A. J., Rawlings, N. D., & Woesner, J. F. (Eds) Academic Press London. pp828-836).

WO 01/70672, WO 02/02512, WO 02/02505 and WO 02/02506 (Elan Pharmaceuticals Inc.) describe a series of hydroxyethylamine compounds having β-secretase activity which are implicated to be useful in the treatment of Alzheimer's disease.

We have found a novel series of compounds which are potent inhibitors of the Asp2 enzyme, thereby indicating the potential for these compounds to be effective in the treatment of disease characterised by elevated β-amyloid levels or β-amyloid deposits, such as Alzheimer's disease.

Thus, according to a first aspect of the present invention we provide a compound of formula (I):



(I)

wherein

R^1 and R^2 independently represent C_{1-3} alkyl, C_{2-4} alkenyl, halogen, C_{1-3} alkoxy, amino, cyano or hydroxy;

m and n independently represent 0, 1 or 2;

p represents 2;

A-B represents $-NR^5-SO_2-$ or $-NR^5-CO-$;

R^5 represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, arylC_{1-6} alkyl-, heteroarylC_{1-6} alkyl, arylC_{3-8} cycloalkyl or heteroarylC_{3-8} cycloalkyl;

X-Y-Z represents $-N-CR^8=CR^{10a}-$;

R^8 represents hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^{10a} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, arylC_{1-6} alkyl-, heteroarylC_{1-6} alkyl, arylC_{3-8} cycloalkyl or heteroarylC_{3-8} cycloalkyl, $-COOR^{12a}$, $-OR^{12a}$, $-CONR^{12a}R^{13a}$, $-SO_2NR^{12a}R^{13a}$, $-COC_{1-6}$ alkyl or $-SO_2C_{1-6}$ alkyl (wherein R^{12a} and R^{13a} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl);

R^3 represents optionally substituted C_{1-6} alkyl, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl, $-C_{1-6}$ alkyl-aryl, $-C_{1-6}$ alkyl-heteroaryl or $-C_{1-6}$ alkyl-heterocyclyl;

R^4 represents hydrogen, optionally substituted C_{1-10} alkyl, -C_{3-8} cycloalkyl, -C_{3-8} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{3-8} cycloalkyl-aryl, -heterocyclyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^aR^b)$-CONH-C_{3-8} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^cR^d, -$C(R^aR^b)$-C_{1-6} alkyl, -$C(R^aR^b)$-aryl, -$C(R^aR^b)$-C_{1-6} alkyl-aryl, -$C(R^aR^b)$-C_{1-6} alkyl-heteroaryl, -$C(R^aR^b)$-C_{1-6} alkyl-heterocyclyl, -C_{1-6} alkyl-O-C_{1-6} alkyl-aryl, -C_{1-6} alkyl-O-C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-O-C_{1-6} alkyl-heterocyclyl;

R^a and R^b independently represent hydrogen, C_{1-6} alkyl or R^a and R^b together with the carbon atom to which they are attached may form a C_{3-8} cycloalkyl or heterocyclyl group;

R^c and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or R^c and R^d together with the nitrogen atom to which they are attached may form a heterocyclyl group;

optional substituents for alkyl groups of R^3 and R^4 include one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano or hydroxy groups;

and wherein said aryl, heteroaryl or heterocyclyl groups of R^3, R^4, R^5 and R^{10a} may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, halogen, -CF_3, -OCF_3, oxo, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, amino, cyano, nitro, -$NR^{22}COR^{23}$, -$CONR^{22}R^{23}$ -C_{1-6} alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl), -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{1-6} alkanoyl or hydroxy groups;

or a pharmaceutically acceptable salt or solvate thereof.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to alkenyl shall be interpreted similarly.

References to C_{3-8} cycloalkyl include references to all alicyclic (including branched) isomers of the corresponding alkyl.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) or carbocyclic benzofused rings (eg. C_{3-8} cycloalkyl fused to a phenyl ring).

References to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-4 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, tetrazolyl and the like. Examples of bicyclic heterocyclic aromatic rings include eg. quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

References to 'heterocyclyl' include references to a 5-7 membered non-aromatic monocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen. Examples of heterocyclic non-aromatic rings include e.g. morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, dioxolanyl, oxathiolanyl, imidazolidinyl, tetrahydropyranyl, pyrazolidinyl and the like.

Preferably, R^5 represents hydrogen, C_{1-6} alkyl (eg. methyl), aryl (eg. phenyl) or C_{1-6} alkylaryl (eg. benzyl).

Preferably, m and n both represent 0.

Preferably, R^8 represents hydrogen.

Preferably, R^{10a} represents hydrogen or C_{1-6} alkyl (eg. ethyl or isopropyl), more preferably ethyl.

Preferably, R^3 represents -C_{1-6} alkyl-aryl (eg. benzyl) optionally substituted by one or two halogen atoms (eg. fluorine). More preferably, R^3 represents unsubstituted benzyl.

Preferably, R^4 represents

-C_{1-10} alkyl (eg. 1,5-dimethylhexyl or 1,1,5-trimethylhexyl);

-C_{3-8} cycloalkyl (eg. cyclopropyl or cyclohexyl);

-$C(R^aR^b)$-aryl (eg. benzyl or 1-phenyl-1-methylethyl) optionally substituted (eg. substituted at the 3 and 5 positions) by one or more halogen, cyano, -OCF_3, -CF_3, C_{1-6} alkyl or C_{1-6} alkoxy (eg. methoxy) groups;

-$C(R^aR^b)$-CONH-C_{3-8} cycloalkyl (eg. $C(R^cR^d)$-CONH-cyclohexyl); or

-C_{3-8} cycloalkyl-aryl.

More preferably, R^4 represents -$C(R^aR^b)$-aryl (eg. benzyl) optionally substituted (eg. substituted at the 3 position) by one or more C_{1-6} alkoxy (eg. methoxy) groups.

Preferably, R^a and R^b independently represent hydrogen, methyl, cyclopropyl or cyclohexyl, more preferably R^a and R^b both represent hydrogen.

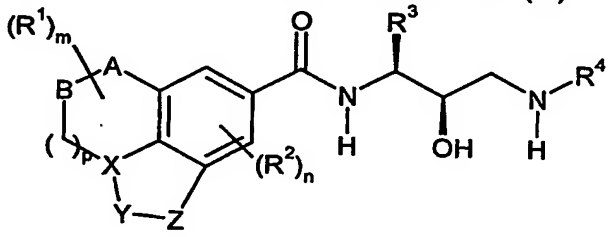
Preferred compounds according to the invention includes examples E1-E4 as shown below, or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, **66**, 1-19, such as acid addition salts formed with inorganic or organic acids e.g.

hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, nitrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, p-toluenesulphonates, naphthalenesulphonates, formates or trifluoroacetates. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. Preferably, compounds of formula (I) are in the form of a single enantiomer of formula (Ia):

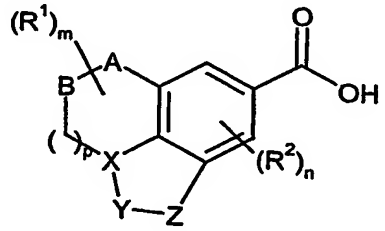


(Ia)

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

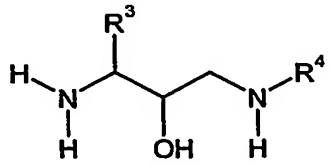
A process according to the invention for preparing a compound of formula (I) which comprises:

(a) reacting a compound of formula (II)



(II)

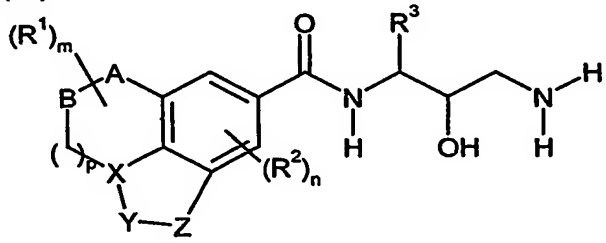
or an activated and/or optionally protected derivative thereof wherein R^1, R^2, m, n, p, A, B, X, Y and Z are as defined above, with a compound of formula (III)



(III)

wherein R^3 and R^4 are as defined above; or

(b) preparing a compound of formula (I) which comprises reductive alkylation of a compound of formula (IV)



(IV)

wherein R^1, R^2, R^3, m, n, p, A, B, X, Y and Z are as defined above, with an appropriate aldehyde or ketone; or

(c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion of compounds of formula (I) to other compounds of formula (I).

Where the compound of formula (II) is an activated derivative, (eg. by activation of a carboxylic acid to an acid chloride, mixed anhydride, active ester e.g. mesylate or tosylate, O-acyl-isourea or other species), process (a) typically comprises treatment of said activated derivative with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid of formula (II) and amine are preferably reacted in the presence of an activating agents such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBT), or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU)

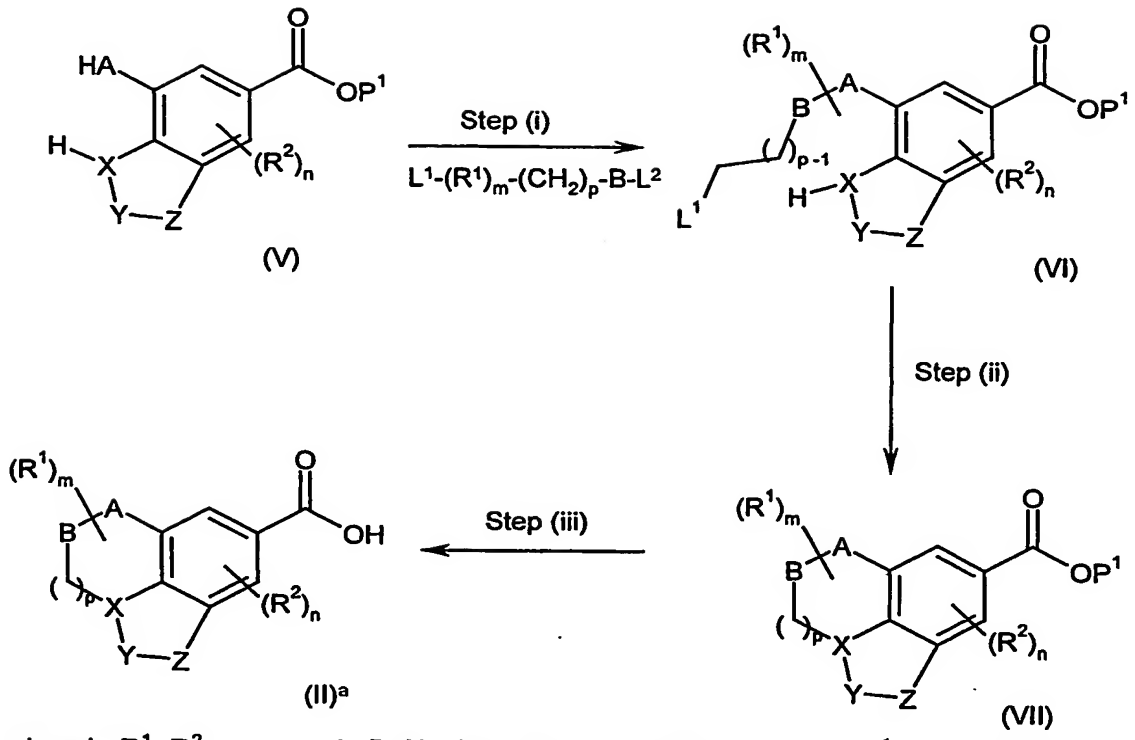
Where the compound of formula (II) is a carboxylic acid, process (a) typically comprises the use of water soluble carbodiimide, HOBT and a suitable base such as tertiary alkylamine or pyridine in a suitable solvent such as DMF and at a suitable temperature, eg. between 0°C and room temperature.

Process (b) typically comprises the use of sodium borohydride triacetate in the presence of a suitable solvent, such as ethanol, dichloromethane and 1,2-dichloroethane and at a suitable temperature, e.g. between 0°C and room temperature.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include aryl sulphonyl (e.g. tosyl), acyl (e.g. acetyl), carbamoyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis. Suitable hydroxy protecting groups would be silyl based groups such as t-butyldimethylsilyl, which may be removed using standard methods, for example use of an acid such as trifluoroacetic or hydrochloric acid or a fluoride source such as tetra n-butylammonium fluoride.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, aromatic substitution, ester hydrolysis, amide bond formation or removal and sulphonylation.

Compounds of formula (II) and/or activated and optionally protected derivatives thereof may be prepared in accordance with the following process:



wherein R^1, R^2, m, n, p, A, B, X, Y and Z are as defined above, P^1 represents a suitable group such as C_{1-6} alkyl, L^1 and L^2 independently represent a suitable leaving group such as a halogen atom (eg. chlorine).

When B represents CO, step (i) typically comprises the use of a suitable base such as triethylamine in the presence of a suitable solvent such as dichloromethane at a suitable temperature, such as room temperature.

When B represents SO_2, step (i) typically comprises the use of a suitable base such as pyridine in the presence of a suitable reagent, eg. DMAP and a suitable solvent such as dichloromethane at a suitable temperature, such as room temperature.

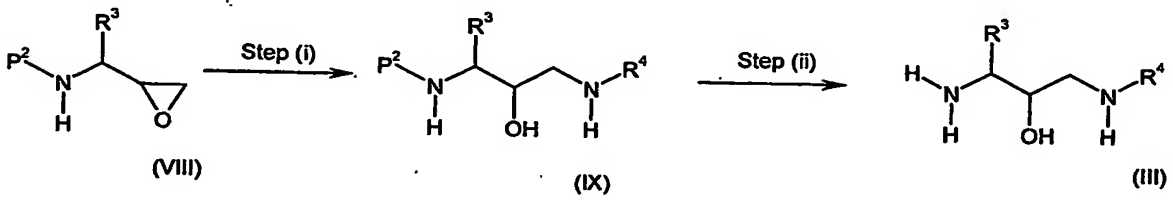
When B represents CO, step (ii) typically comprises the use of sodium hydride in the presence of a suitable solvent, eg. dimethylformamide at a suitable temperature, eg. 100°C.

When B represents SO_2, step (ii) typically comprises the use of a suitable base such as triethylamine in the presence of a suitable solvent such as dichloromethane at a suitable temperature, such as room temperature, followed by a subsequent reaction with sodium hydride in the presence of a suitable solvent, eg. dimethylformamide at a suitable temperature, eg. 100°C.

Step (iii) typically comprises a standard procedure for conversion of a carboxylic ester to an acid, such as the use of an appropriate hydroxide salt like lithium or sodium salt in an

appropriate solvent such as methanol at an appropriate temperature such as room temperature. In the case of a tert-butyl ester this conversion can be achieved by the use of an appropriate acid such as trifluoroacetic acid in an appropriate solvent such as dichloromethane at an appropriate temperature such as O°C. Activated derivatives of compounds of formula (II) may then be prepared as described in process (a) above.

Compounds of formula (III) may be prepared in accordance with the following process:



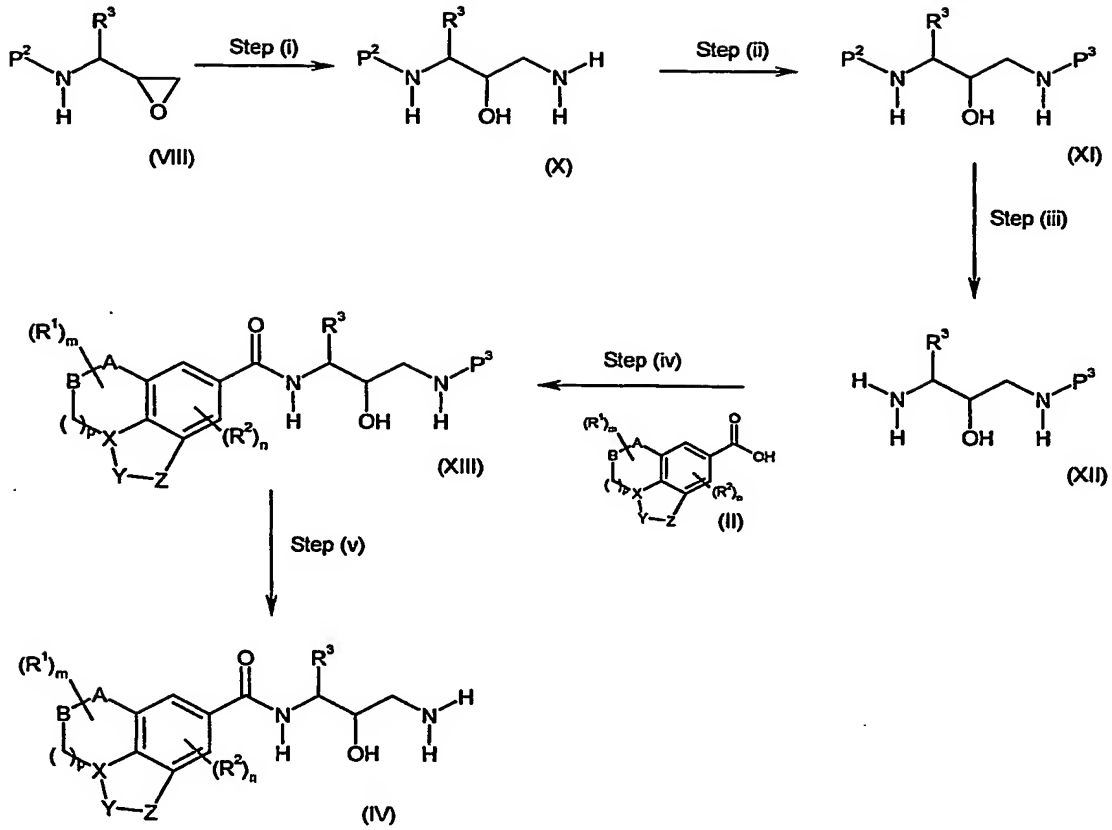
(VIII) (IX) (III)

wherein R^3 and R^4 are as defined above and P^2 represents a suitable amine protecting group, such as t-butoxycarbonyl.

Step (i) typically comprises the reaction of a compound of formula (VIII) with a compound of formula NH_2R^4 in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

Step (ii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^2 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Compounds of formula (IV) may be prepared in accordance with the following process:



wherein R^1, R^2, R^3, m, n, p, A, B, X, Y, Z and P^2 are as defined above and P^3 represents a suitable amine protecting group different to P^2, such as -$COOCH_2$-phenyl.

Step (i) typically comprises the reaction of a compound of formula (VIII) in aqueous ammonia in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

When P^3 represents -$COOCH_2$-phenyl, step (ii) typically comprises the use of $ClCOOCH_2$-phenyl in the presence of a suitable base, e.g. triethylamine, a suitable solvent, e.g. dimethylformamide at a suitable temperature, e.g. between 0°C and room temperature.

Step (iii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^2 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Step (iv) typically comprises reacting a compound of formula (XI) with a compound of formula (II) in the presence of water soluble carbodiimide and HOBT.

Step (v) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^3 represents -$COOCH_2$-phenyl, deprotection typically comprises the use of a suitable catalyst, eg. palladium in the presence of a suitable solvent, e.g. water and ethanol and in the presence of a suitable hydrogen source, e.g. ammonium formate at a suitable temperature, eg. 60°C.

Compounds of formula (V) and (VIII) are either commercially available or may be prepared from commercially available compounds using standard procedures.

As a further aspect of the invention there is thus provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical, particularly in the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with diseases characterised by elevated β-amyloid levels or β-amyloid deposits, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

As a further aspect of the invention there is thus provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in the therapy of diseases characterised by elevated β-amyloid levels or β-amyloid deposits, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

It will be appreciated that diseases characterised by elevated β-amyloid levels or β-amyloid deposits include Alzheimer's disease, mild cognitive impairment, Down's syndrome, hereditary cerebral haemorrhage with β-amyloidosis of the Dutch type, cerebral β-amyloid angiopathy and various types of degenerative dementias, such as those associated with Parkinson's disease, progressive supranuclear palsy, cortical basal degeneration and diffuse Lewis body type of Alzheimer's disease.

Most preferably, the disease characterised by elevated β-amyloid levels or β-amyloid deposits is Alzheimer's disease.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

Compounds of formula (I) may be used in combination with other therapeutic agents. Suitable examples of such other therapeutic agents may be acetylcholine esterase inhibitors, gamma secretase inhibitors, anti-inflammatory agents such as cyclooxygenase II inhibitors, antioxidants or p-glycoprotein (P-gp) inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, enteral, parenteral, topical, sublingual, intrathecal or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may

also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.
For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

When the compounds of the invention are administered topically they may be presented as a cream, ointment or patch.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 3000 mg; and such unit doses may be administered more than once a day, for example one, two, three or four times per day (preferably once or twice); and such therapy may extend for a number of weeks, months or years.

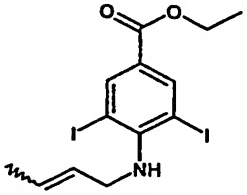
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Examples

Preparation of Intermediates

Description 1

4-((Z/E)-But-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (D1)



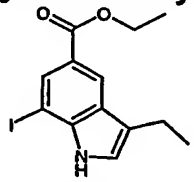
To a solution of 4-amino-3,5-diiodo-benzoic acid ethyl ester (commercially available from Maybridge) (72.6 g, 0.17 mmol, 1 equiv) in DMF (450 ml) at 0°C under nitrogen was added NaH (60% in mineral oil, 7.3 g, 0.18 mmol, 1.05 equiv) portionwise over 2 min. After 10 min crotyl bromide (21.5 ml, 0.21 mmol, 1.2 equiv) in DMF (50 ml) was added *via cannula* over 5 min and the resulting mixture was allowed to warm to room temperature over 30 min. 5 ml of EtOH were added and the mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O. The aqueous phase was extracted with AcOEt and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (D1) (82 g, 100%) as a pink solid which was used in the next step without further purification.

$[M+H]^+ = 472.0$

RT = 4.93 min.

Description 2

3-Ethyl-7-iodo-1 *H*-indole-5-carboxylic acid ethyl ester (D2)



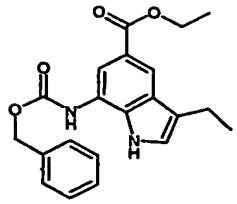
To a solution of 4-((Z/E)-but-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (D1) (15 g, 31.8 mmol, 1 equiv) in DMF (150 ml) at room temperature under nitrogen were added $Pd(OAc)_2$ (357 mg, 1.6 mmol, 0.05 equiv), NaCOOH (6.5 g, 95.6 mmol, 3 equiv), Na_2CO_3 (8.4 g, 79.6 mmol, 2.5 equiv) and Nbu_4Cl (8.0 g, 35.0 mmol, 1.1 equiv). The resulting suspension was stirred under nitrogen at 80°C for 30 min then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 9/1) gave the title compound (D2) (6.3 g, 58%) as a white solid.

$[M+H]^+ = 344.0$

RT = 3.86 min.

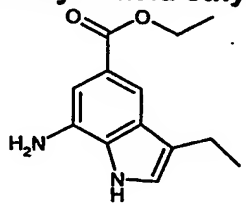
Description 3

7-Benzyloxycarbonylamino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D3)



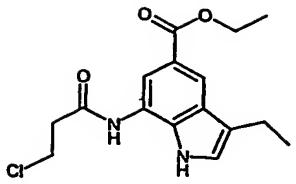
To a solution of 3-ethyl-7-iodo-1 *H*-indole-5-carboxylic acid ethyl ester (D2) (850 mg, 2.48 mmol, 1 equiv) in toluene (20 ml) at room temperature under nitrogen were added benzyl carbamate (562 mg, 3.72 mmol, 1.5 equiv), copper iodide (24 mg, 0.13 mmol, 0.05 equiv) K_3PO_4 (1.05 g, 4.8 mmol, 2 equiv) and N,N'-dimethylethylenediamine (26 µl, 0.25 mmol, 0.1 equiv) and the resulting suspension was stirred at 100°C for 30 min then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 9/1) gave the title compound (D3) (250 mg, 27%) as an off white solid.
$[M+H]^+ = 367.1$
RT = 3.73 min.

Description 4
7-Amino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D4)



To a solution of 7-benzyloxycarbonylamino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D3) (250 mg, 0.68 mg, 1 equiv) in EtOH (10 ml) were added NH_4COOH (431 mg, 6.8 mmol, 10 equiv), H_2O (2 ml), Pd (10% w/w on charcoal, 50 mg, 0.02 equiv w/w) and the resulting mixture was stirred at 70°C for 1.5 h. Another 200 mg of Pd (10% w/w on charcoal, 0.08 equiv w/w) were then added and the resulting mixture stirred at 70°C for another 30 min then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the EtOH was removed *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (D4) (150 mg, 95%) as an off white solid which was used in the next step without further purification.
$[M+H]^+ = 233.1$
RT = 3.19 min.

Description 5
7-(3-Chloro-propanoylamino)-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D5)



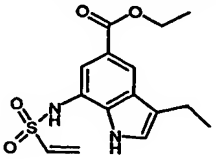
To a solution of 7-amino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D4) (300 mg, 1.29 mmol, 1 equiv) in CH_2Cl_2 (10 ml) were added NEt_3 (216 µl, 1.55 mmol, 1.2 equiv) and 3-chloropropionyl chloride (136 µl, 1.42 mmol, 1.1 equiv) and the resulting solution was stirred at room temperature for 48 h then diluted with AcOEt and washed with H_2O. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1) gave the title compound (D5) (300 mg, 72%) as a white solid.

$[M+H]^+ = 323.4$

RT = 3.18 min.

Description 6

7-Ethenesulfonylamino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D6)



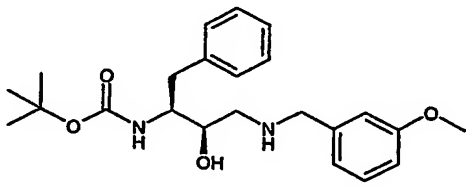
To a solution of 7-amino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D4) (1.1 g, 4.74 mmol, 1 equiv) in CH_2Cl_2 (20 ml) at room temperature were added pyridine (575 µl, 7.11 mmol, 1.5 equiv), DMAP (66 mg, 0.47 mmol, 0.1 equiv) and 2-chloroethanesulfonyl chloride (545 µl, 5.22 mmol, 1.1 equiv) and the resulting mixture was stirred for 5 min then diluted with AcOEt. The organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 ml) and NEt_3 (1 ml, excess) was added and the resulting solution was stirred at room temperature for 16 h then diluted with AcOEt. The organic phase was washed with H_2O, 2N aqueous HCl solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude title compound (D6) (1.7 g, 110%) as a brown oil which was used in the next step without further purification.

$[M+H]^+ = 323.1$

RT = 3.29 min.

Description 7

[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (D7)

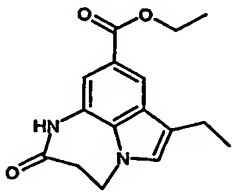


((S)-(S)-1-Oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (10 g, 38 mmol, 1 equiv) [Chirex 1819W94 Lot#9924382] was dissolved in EtOH (100 ml) and 3-methoxy-benzylamine (14.6 ml, 114 mmol, 3 equiv) was added. The resulting mixture was heated, under an atmosphere of nitrogen, for 12 h at reflux temperature. The mixture was cooled and the solvent was removed by evaporation *in vacuo*. The residue was dissolved in AcOEt and washed three times with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH: 98/2 to 95/5) gave the title compound (D7) (10.0 g, 66%) as a white solid.

Preparation of Esters

Ester 1

7-Ethyl-2-oxo-1,2,3,4-tetrahydro-[1,4]diazepino[3,2,1-*hi*]indole-9-carboxylic acid ethyl ester (C1)



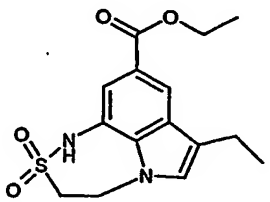
To a solution of 7-(3-chloro-propanoylamino)-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D5) (300 mg, 0.93 mmol, 1 equiv) in DMF (10 ml) at room temperature under nitrogen was added NaH (60% in mineral oil, 41 mg, 1.02 mmol, 1.1 equiv). The resulting solution was heated to 100°C for 1 h and then cooled to room temperature. Excess NaH was neutralised with EtOH (2 ml) and the solution was concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 2/3) gave the title compound (C1) (120 mg, 45%) as a white solid.

$[M+H]^+ = 287.0$

RT = 3.08 min.

Ester 2

2-Ethyl-7,7-dioxo-6,7,8,9-tetrahydro-7λ^6-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid ethyl ester (C2)



To a solution of 7-ethenesulfonylamino-3-ethyl-1 *H*-indole-5-carboxylic acid ethyl ester (D6) (130 mg, 0.4 mmol, 1 equiv) in DMF (10 ml) at room temperature under nitrogen was added NaH (60% in mineral oil, 19 mg, 0.45 mmol, 1.2 equiv). After 5 min, the

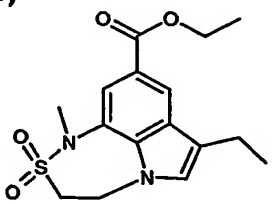
mixture was heated to 100°C for 1 h and then cooled to room temperature. EtOH (1 ml) was added and the solution was diluted with AcOEt. The organic phase was washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (C2) (100 mg, 77%) as a brown solid which was used in the next step without further purification.

$[M+H]^+$ = 323.3

RT = 2.93 min.

Ester 3

2-Ethyl-6-methyl-7,7-dioxo-6,7,8,9-tetrahydro-7*l*^{6}-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid ethyl ester (C3)



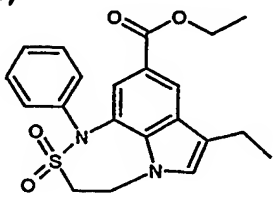
To a solution of 2-ethyl-7,7-dioxo-6,7,8,9-tetrahydro-7*l*^{6}-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid ethyl ester (C2) (200 mg, 0.621 mmol, 1 equiv) in DMF (10 ml) at room temperature under nitrogen were added NaH (60% in mineral oil, 50 mg, 1.24 mmol, 2 equiv) and, after 2 min, MeI (46 µl, 0.74 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature for 30 min then EtOH (1 ml) was added and the solution concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 1/1) gave the title compound (C3) (150 mg, 76%) as a white solid.

$[M+H]^+$ = 337.1

RT = 3.24 min.

Ester 4

2-Ethyl-7,7-dioxo-6-phenyl-6,7,8,9-tetrahydro-7*l*^{6}-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid ethyl ester (C4)



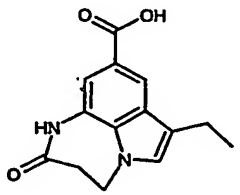
To a solution of 2-ethyl-7,7-dioxo-6,7,8,9-tetrahydro-7*l*^{6}-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid ethyl ester (C2) (200 mg, 0.62 mmol, 1 equiv) in CH_2Cl_2 (30 ml) were added phenylboronic acid (312 mg, 2.5 mmol, 4 equiv), copper (II) acetate (220 mg, 1.25 mmol, 2 equiv), NEt_3 (350 ml, 2.5 mmol, 4 equiv) and activated 4A molecular sieves (300 mg). The resulting mixture was stirred at room temperature for 2 h and then filtered. The filtrate was washed with 2N aqueous HCl solution, a 2N

aqueous NaOH solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 2/1) gave the title compound (C4) (30 mg, 12%) as a white solid.
$[M+H]^+$ = 399.2
RT = 3.54 min.

Preparation of Acids

Acid 1

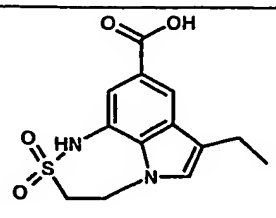
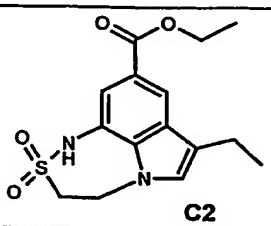
7-Ethyl-2-oxo-1,2,3,4-tetrahydro-[1,4]diazepino[3,2,1-*hi*]indole-9-carboxylic acid (A1)

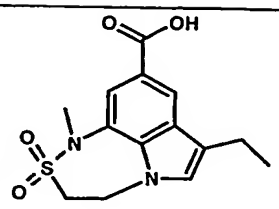
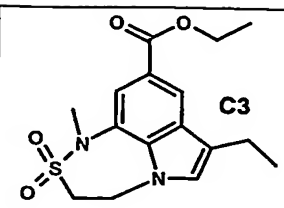
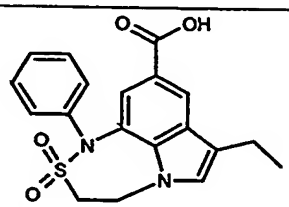
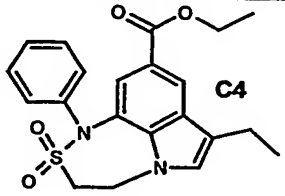


To a solution 7-ethyl-2-oxo-1,2,3,4-tetrahydro-[1,4]diazepino[3,2,1-*hi*]indole-9-carboxylic acid ethyl ester (C1) (120 mg, 0.42 mmol, 1 equiv) in EtOH (20 ml) was added 2N aqueous NaOH solution (20 ml, 40 mmol, 95 equiv). The resulting mixture was stirred for 14 h then most of EtOH was removed *in vacuo*. The residue was extracted with Et_2O. The aqueous layer was acidified using 2N aqueous HCl solution and the white precipitate formed was extracted twice with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (A1) (62 mg, 57%) as a white solid, which was used in the next step without further purification.
$[M+H]^+$ = 259.4
RT = 2.56 min

Acids 2-4 (A2-A4)

Acids 2-4 were obtained from the corresponding esters using an analogous procedure to that described for Acid 1:

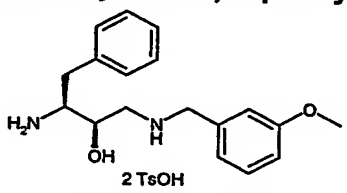
Acid	Structure	Starting Material	$[M+H]^+$	RT (min)
2-Ethyl-7,7-dioxo-6,7,8,9-tetrahydro-7*l*^{6}-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid (A2)		 C2	293.2	2.55

2-Ethyl-6-methyl-7,7-dioxo-6,7,8,9-tetrahydro-7*l*^{6}-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid (A3)		 C3	309.1	2.68
2-Ethyl-7,7-dioxo-6-phenyl-6,7,8,9-tetrahydro-7*l*^{6}-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid (A4)		 C4	371.1	3.14

Preparation of Bases

Base 1

(2R,3S)-3-Amino-1-(3-methoxy-benzylamino)-4-phenyl-butan-2-ol di-tosylate (B1)

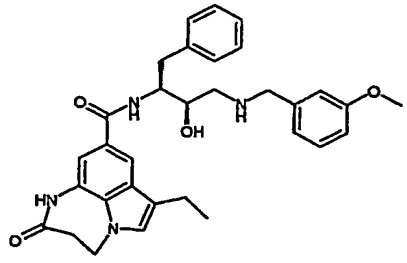


To a solution of [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (D7) (10 g, 25 mmol, 1 equiv) in CH_3CN (100 ml) was added PTSA.H_2O (14 g, 75 mmol, 3 equiv) and the resulting mixture was stirred for 16 h. The white precipitate formed was filtered and washed with Et_2O then dried under vacuum to give the title compound (B1) (15.6 g, 92%) which was used in the next step without further purification.

Examples

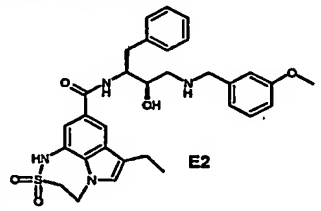
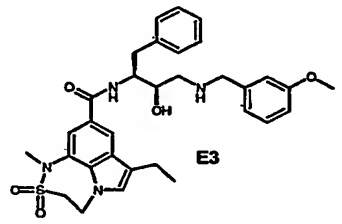
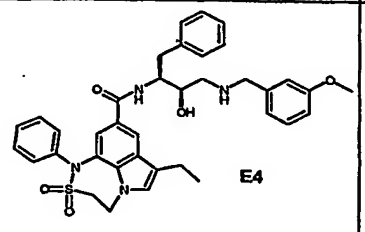
Example 1

7-Ethyl-2-oxo-1,2,3,4-tetrahydro-[1,4]diazepino[3,2,1-*hi*]indole-9-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide (E1)



To a solution of 7-ethyl-2-oxo-1,2,3,4-tetrahydro-[1,4]diazepino[3,2,1-*hi*]indole-9-carboxylic acid (A1) (31 mg, 0.12 mmol, 1 equiv) in DMF (2 ml) and CH_2Cl_2 (8 ml) at room temperature was added (2R,3S)-3-amino-1-(3-methoxy-benzylamino)-4-phenyl-butan-2-ol di-tosylate (B1) (77 mg, 0,12 mmol, 1 equiv), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (28 mg, 0.15 mmol, 1.2 equiv), 1-hydroxybenzotriazole hydrate (22 mg, 0.15 mmol, 1.2 equiv) and 4-ethylmorpholine (34 µl, 0.27 mmol, 2.2 equiv). The resulting mixture was stirred for 4 h then a saturated aqueous $NaHCO_3$ solution (10 ml) was added. The resulting mixture was vigorously stirred for 20 min. The layers were separated through an hydrophobic frit and the organic phase was concentrated *in vacuo*. The residue was purified by trituration with Et_2O to yield the title compound (E1) as a white solid (43.5 mg, 67 %).
$[M+H]^+$ = 541.5
RT = 2.51 min.

Examples 2-4 (E2-E4)
Examples 2-4 were obtained in an analogous procedure to that described for Example 1 using the appropriate acid and the appropriate amine indicated in the table below:

Example	Structure	Acid	Base	$[M+H]^+$	RT
2-Ethyl-7,7-dioxo-6,7,8,9-tetrahydro-7λ^6-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide (E2)	 E2	A2	B1	577.4	2.52
2-Ethyl-6-methyl-7,7-dioxo-6,7,8,9-tetrahydro-7λ^6-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide (E3)	 E3	A3	B1	591.4	2.60
2-Ethyl-7,7-dioxo-6-phenyl-6,7,8,9-tetrahydro-7λ^6-thia-6,9a-diaza-benzo[*cd*]azulene-4-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide (E4)	 E4	A4	B1	653.3	2.85

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assay:

Asp-2 inhibitory assay

For each compound being assayed, in a 384 well plate, is added:-

a) 1μl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 μM).

b) 10 μl of substrate (FAM-[SEVNLDAEFK]-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid). Aminomethyl fluorescein (FAM) and tetramethyl rhodamine (TAMRA) are fluorescent molecules which co-operate to emit fluorescence at 535nm upon cleavage of the SEVNLDAEFK peptide.

c) 10 μl enzyme solution. This is prepared by diluting 16ml of a 500nM enzyme solution into 384 ml of buffer (prepared as above).

Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

Pharmacological Data

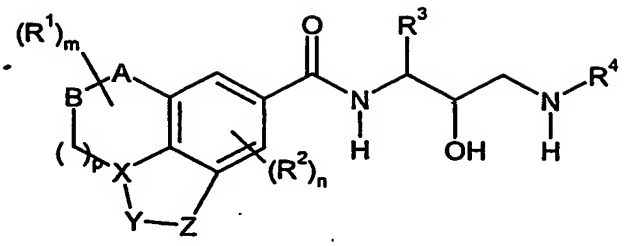
The compounds of E1-E4 were tested in the Asp-2 inhibitory assay and exhibited inhibition <10μM. More particularly, the compounds of Examples E2-E4 exhibited inhibition <1μM.

Abbreviations

DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMAP	dimethylaminophenol
DABCO	1,4-diazabicyclo [2.2.2] octane
DME	dimethyl ether
THF	tetrahydrofuran
HOBT	N-hydroxybenzotriazole
FAM	carboxyfluorescein
TAMRA	carboxytetramethylrhodamine
[ ]	single amino acid letter code relating to peptide sequence

Claims

1. A compound of formula (I):



(I)

wherein

R^1 and R^2 independently represent C_{1-3} alkyl, C_{2-4} alkenyl, halogen, C_{1-3} alkoxy, amino, cyano or hydroxy;

m and n independently represent 0, 1 or 2;

p represents 2;

A-B represents $-NR^5-SO_2-$ or $-NR^5-CO-$;

R^5 represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, arylC_{1-6} alkyl-, heteroarylC_{1-6} alkyl, arylC_{3-8} cycloalkyl or heteroarylC_{3-8} cycloalkyl;

X-Y-Z represents $-N-CR^8=CR^{10a}-$;

R^8 represents hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^{10a} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heteroaryl, arylC_{1-6} alkyl-, heteroarylC_{1-6} alkyl, arylC_{3-8} cycloalkyl or heteroarylC_{3-8} cycloalkyl, $-COOR^{12a}$, $-OR^{12a}$, $-CONR^{12a}R^{13a}$, $-SO_2NR^{12a}R^{13a}$, $-COC_{1-6}$ alkyl or $-SO_2C_{1-6}$ alkyl (wherein R^{12a} and R^{13a} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl);

R^3 represents optionally substituted C_{1-6} alkyl, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl, $-C_{1-6}$ alkyl-aryl, $-C_{1-6}$ alkyl-heteroaryl or $-C_{1-6}$ alkyl-heterocyclyl;

R^4 represents hydrogen, optionally substituted C_{1-10} alkyl, $-C_{3-8}$ cycloalkyl, $-C_{3-8}$ cycloalkenyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl, $-C_{3-8}$ cycloalkyl-aryl, -heterocyclyl-aryl, $-C_{1-6}$ alkyl-aryl-heteroaryl, $-C(R^aR^b)-CONH-C_{1-6}$ alkyl, $-C(R^aR^b)-CONH-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl-S-C_{1-6} alkyl, $-C_{1-6}$ alkyl-NR^cR^d, $-C(R^aR^b)-C_{1-6}$ alkyl, $-C(R^aR^b)$-aryl, $-C(R^aR^b)-C_{1-6}$ alkyl-aryl, $-C(R^aR^b)-C_{1-6}$ alkyl-heteroaryl, $-C(R^aR^b)-C_{1-6}$ alkyl-heterocyclyl, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl-aryl, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl-heteroaryl or $-C_{1-6}$ alkyl-O-C_{1-6} alkyl-heterocyclyl;

R^a and R^b independently represent hydrogen, C_{1-6} alkyl or R^a and R^b together with the carbon atom to which they are attached may form a C_{3-8} cycloalkyl or heterocyclyl group;

R^c and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or R^c and R^d together with the nitrogen atom to which they are attached may form a heterocyclyl group;

optional substituents for alkyl groups of R^3 and R^4 include one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano or hydroxy groups;

and wherein said aryl, heteroaryl or heterocyclyl groups of R^3, R^4, R^5 and R^{10a} may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, halogen, $-CF_3$, $-OCF_3$, oxo, C_{1-6} alkoxy, C_{2-6} alkynyl, C_{2-6} alkenyl, amino, cyano, nitro, $-NR^{22}COR^{23}$, $-CONR^{22}R^{23}$ $-C_{1-6}$ alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl), $-C_{1-6}$ alkyl-O-C_{1-6} alkyl, $-C_{1-6}$ alkanoyl or hydroxy groups; or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 which is a compound of formula E1-E4 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

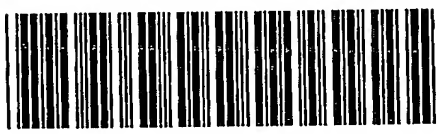
4. A compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

5. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

6. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

7. A method of treatment or prophylaxis of diseases characterised by elevated β-amyloid levels or β-amyloid deposits which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof.

8. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.



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